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NORMAL SPATIAL MEMORY FOLLOWING POSTSEIZURE TREATMENT WITH KETAMINE: SELECTIVE DAMAGE ATTENUATES MEMORY DEFICITS IN BRAIN-DAMAGED RODENTS*

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Within 30 min after the initiation of status epilepticus (SE) by lithium and pilocarpine, rats were injected with either acepromazine or ketamine. Compared to the rats that had received the acepromazine, the group that had received the ketamine displayed more accurate spatial memory. Their scores did not differ significantly from normal (non-seized) controls. Although the ketamine treatment did not significantly change the amount of neuronal loss within about 100 Paxinos and Watson structures, it was neuroprotective for several structures within the thalamus and portions of the temporal and parietal cortices. Ketamine-treated rats, however, displayed markedly more damage within the entorhinal cortices and amygdalohippocampal area.

Keywords: Seizure; Spatial memory; Ketamine; Brain-damage; Rat

INTRODUCTION

The relationships between the structural organizations of the brain and behavior have been discerned by focal lesions induced by exogenous sources such as electrodes or (aspiration) pipettes.

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Persinger *et al.* (1994) suggested that quantification of the patterns of neuronal damage from endogenous sources, such as those generated by the excitotoxic and apoptotic consequences of sustained seizures, should both reaffirm and extend the results of single-lesion experiments. This suggestion has been supported by the direct comparisons between the behavioral changes subsequent to lesions produced by exogenous sources and the behavioral changes subsequent to "autolesions" from endogenous sources (Harrigan *et al.*, 1991; Peredery *et al.*, 1992; Persinger *et al.*, 1997, 1998).

Recently we have found that different drugs injected within a few minutes to two hours after the induction of limbic seizures (Honchar *et al.*, 1983) by a subcutaneous injection of 3 mEq/kg of lithium chloride followed 4 hrs later by a subcutaneous injection of 30 mg/kg of pilocarpine resulted in different amounts of neuronal loss within different structures of the rat brain. To date we have studied the effects of prazosin, acepromazine, arginine, and ketamine. We have been pursuing the hypothesis that experimental creations of different, reliable patterns of multifocal damage might allow greater understanding of the quantitative relationships between aggregates of discrete brain structures and behavior.

The following experiment was designed to discern if a single injection of ketamine (Fujikawa, 1995, 1996) rather than acepromazine (Persinger *et al.*, 1993) 30 min after the overt display of limbic seizures induced by a single systemic injection of lithium and pilocarpine: (1) attenuated the severe deficits in spatial memory, and, (2) selectively spared traditional nuclei (Paxinos and Watson, 1986) within which neuronal drop-out and gliosis have been prominent for rats with this history. We expected a strong quantitative relationship existed between the proportions of neuronal sparing relative to non-treated brains and the accuracy of memory for a spatial task.

MATERIALS AND METHODS

Twenty-one (21) male albino Wistar rats, approximately 100 days old, were habituated (two weeks) to the colony conditions which were a light : dark cycle of 12 : 12 hrs (onset 0800 hrs) and room temperature, controlled by thermostat, between 20 and 21°C.

Each rat was injected subcutaneously in the right flank with 3 mEq/kg of the lithium chloride. Four hours later, the rats were injected with 30 mg/kg of pilocarpine. Within 30 to 40 min all rats, after progressing through successive stages of head nodding and myoclonic displays, the usual Level 5 Racine (1972) seizures were exhibited. It was characterized by a conspicuous and discrete rapid forepaw clonus, rearing and falling followed by SE. The behaviours were identical to those associated with concomitant paroxysmal activity within the brain (Handforth and Treiman, 1995).

Thirty minutes after the onset of the Racine Level 5 seizures (rearing, rapid forepaw clonus and falling), 9 rats were injected s.c. between the shoulders with 25 mg/kg of acepromazine (Ayerst Pharmaceutical, Montreal) while another 6 rats had been injected with 100 mg/kg of ketamine. (More, *i.e.*, 10, rats were injected with acepromazine in anticipation of the occasional mortality that occurs following the induction of the protracted seizures by lithium/pilocarpine.) The rats were then returned to their home cages and were given food mush during the subsequent three to four days (Persinger *et al.*, 1993).

One month later, these rats as well as six age-matched controls were slowly reduced to 80% body weight over a 7 to 10 day period. They were given 10 successive days of training and testing within an Olton maze (Olton *et al.*, 1979). The same four arms of this eight-arm maze always contained reward (two fruit loops) while the adjacent arms did not. Each rat was allowed 15 min per day within the maze. The numbers of times the rat re-entered an arm in which there had been a reward were considered working (short-term) memory errors while entries into arms that had never been baited (rewards present) were defined as reference (long-term) memory errors. The average numbers of working and reference errors for the 10 days were calculated as the index of each rat's proficiency.

Within 48 hrs after completion of the maze (about 40 days after the induction of the seizures), the brains were quickly removed, fixed for several weeks in ethanol-formalin-acetic acid (EFA) and processed. Ten micrometer coronal sections, every 100 um between the posterior and anterior commissure were obtained and stained with toluidine blue O. This combination of fixative and stain produce clear cellular detail at both 200X and 400X (Persinger, 1979).

The proportion of damage within all of the Paxinos and Watson structures that are contained within the boundary of the two commissures were discerned by dividing the number of sections that contained necrosis, which was clearly defined by neuronal dropout, within a structure by the total number of sections examined for that structure. Assessment of damage was completed separately for each structure within the left and the right side of the brain by the second author who did not know the treatment condition for each rat. The reliability and validity of this measurement procedure has been indicated by the strong correlations between the proportion of damage scores and behavioral measures such as conditioned taste aversion and proficiency of acquisition of an automated maze (Persinger *et al.*, 1994).

One way analyses of variance were completed between the brains of rats that had received the ketamine or the acepromazine for the proportion of damage in all structures. Because of the sample size and likelihood of spurious significance considering the numbers of structures that were counted (n about 150) for each side of the brain the probability value was set at $< .01$. To discern the effect size, defined as the amount of variance in neuronal dropout accommodated by the treatments, η^2 values (equivalent to the r^2, *i.e.*, the coefficient of determination) were also obtained.

A two-way analysis of variance with one level repeated (reference memory errors *vs.* working memory errors) and one not repeated (ketamine, acepromazine, controls) was completed for the mean numbers of errors for the 10 days of testing. *Post hoc* analysis (Scheffe's $p < .05$) were completed where appropriate. Analyses of variance and covariance between the maze data and the amount of damage within implicated structures and between the structures that displayed the greatest damage were completed in order to suggest sources for the treatment effects. These and related analyses involved SPSS software on a Vax 4000 computer.

RESULTS

The means and standard deviations for the average numbers of working memory errors and reference memory errors for the three groups are shown in Figure 1. The results of the two way analysis of

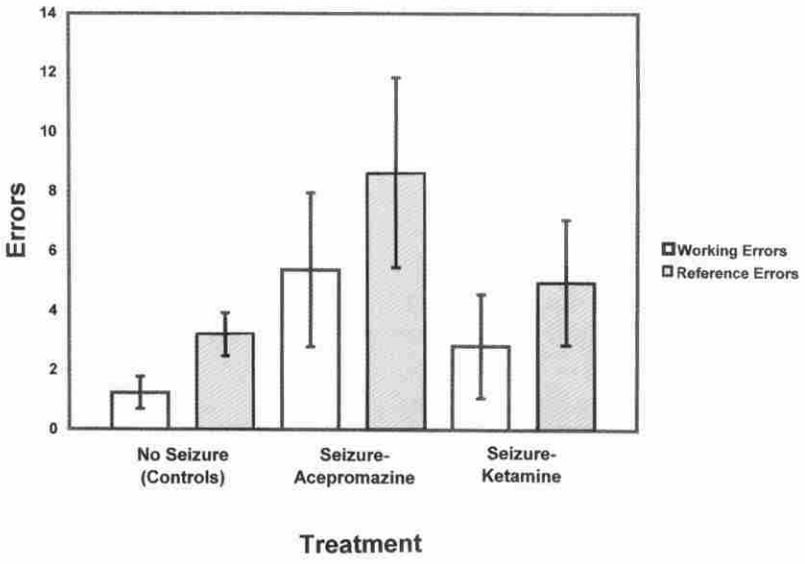

FIGURE 1 Means and standard deviations for the mean numbers of working memory errors and reference memory errors in a radial arm maze over ten days for rats that had been seized by lithium/pilocarpine and treated with either acepromazine or ketamine. Values for normal (control) rats are also shown.

variance with one level repeated (reference *vs.* working errors) demonstrated statistically significant differences ($F(2,18) = 9.99$, $p = .001$; $\eta^2 = 53\%$) between treatments (control, seized-acepromazine and seized-ketamine) for the combination of working and reference errors. *Post hoc* analysis (Scheffe, $p < .05$) indicated rats that had been seized and had received the acepromazine displayed more errors relative to the group that had been seized and received the ketamine. The errors for the latter group did not differ significantly from the normal rats. All groups displayed significantly ($F(1,18) = 62.85$, $p < .001$) more errors for reference memory compared to working memory. The interaction between the types of memory errors and the treatments was not significant statistically ($F(2,18) = 1.95$, $p > .05$).

Whereas the seized rats that had received the acepromazine (our typical procedure) were hyper-responsive and aggressive, the rats in which seizures had been induced but then had received the ketamine were handled easily. Qualitatively, the rats that had received the ketamine did not differ from normal rats.

The means and standard deviations for the proportions of neuronal loss within only those structures that displayed differences of $p < .01$ between the ketamine and acepromazine treatments are shown in Tables I and II, for the left and right sides of the brain, respectively. The approximately 115 structures that exhibited neuronal loss but whose scores did not differ between the groups are not shown. The magnitude of the damage within these structures did not differ by more than 5% from those reported elsewhere (Persinger *et al.*, 1994). These means and standard deviations, respectively, for these scores (ketamine and acepromazine combined) ranged from 15 and 30 for the gustatory nucleus of the thalamus to 81 and 10 for the posteriomedial corticoamygdaloid nucleus.

The effect sizes (η^2 values) that reflect the amount of variability in the histological scores accommodated (explained) by the treatments are also shown for the structures. The strongest and most significant ($p < .001$) treatment differences were noted for the amygdaloid-hippocampal transition area, the ventral reuniens of the thalamus, the lateral posteriomedial nucleus (rostral part) and the lateral dorsal

TABLE I Means and standard deviations for the proportion of damage within left hemispheric structures (Paxinos and Watson abbreviations) that displayed significant ($p < .01$) differences between rats that had been treated with either acepromazine or ketamine after induction of lithium/pilocarpine seizures. The amount of variance explained by the treatments (η^2) is also shown

	Acepromazine		*Ketamine*		η^2
Structure	*M*	*SD*	*M*	*SD*	(%)
All Damage	19	7	14	3	–
Entorhinal Ctx	35	37	82	14	36
Entorhinal Ctx (medial)	38	32	78	18	36
Parietal Ctx Area 1	65	31	17	16	52
Amygdalohippocampal area (posteriormedial)	9	13	67	28	69
amygdalohippocampal area (anterolateral)	9	18	58	37	48
Thalamus					
Supragenicular nuc.	40	15	10	25	38
Posterior nuc. grp.	87	10	50	35	52
Laterordorsal thalamus (ventrolateral part)	73	27	8	13	68
Centrolateral nuc.	76	35	17	40	41
Paracentral nuc.	56	41	0	0	45
Reuniens (ventral part)	81	22	8	20	67
Mediodorsal nuc.	89	22	25	41	53
Mediodorsal nuc. (lateral part)	82	27	25	41	45
Anteriormedial nuc.	61	48	0	0	41

TABLE II Means and standard deviations for the proportion of damage within right hemispheric structures (Paxinos and Watson abbreviations) that displayed significant ($p < .01$) differences between rats that had been treated with either acepromazine or ketamine after induction of lithium/pilocarpine seizures. The amount of variance explained by the treatments (η^2) is also shown

	Acepromazine		*Ketamine*		η^2
Structure	*M*	*SD*	*M*	*SD*	(%)
All Damage	20	8	13	3	15
Entorhinal Ctx (medial)	34	32	78	21	38
Temporal Ctx (area 2)	34	22	0	0	50
Parietal Ctx (area 2)	59	41	8	9	40
Amygdalohippocampal area (posteromedial part)	8	23	80	22	72
Thalamus					
Medial geniculate (dorsal)	27	13	5	12	43
Posterior nuc. grp.	89	17	45	29	52
Lateroposterior nuc. (mediorostral part)	78	26	13	24	64
Laterodorsal nuc. (ventrolateral part)	83	21	17	25	71
Laterodorsal nuc. (dorsomedial part)	84	23	21	25	66
Paracentral nuc.	50	37	0	0	45
Reuniens (ventral)	87	27	10	16	74
Mediodorsal (lateral)	78	27	30	40	36
Mediodorsal (medial)	83	35	22	40	43

nucleus, ventrolateral part. Whereas the ketamine treatment, compared to the acepromazine treatment, preserved neurons within these thalamic structures this same compound exacerbated damage within the amygdalohippocampal area and the entorhinal cortices.

Factor analysis (PA 1 method) of these two thalamic nuclei and the amydalohippocampal area for the right hemisphere and the nucleus reuniens (technically a central structure) indicated (only one factor emerged) that damage in all four structures was related to a shared source of variance (eigen value = 3.17; 79% of variance explained). Discriminant analysis indicated that the amount of damage within the ventral nucleus reuniens, singly, accurately classified (canonical correlation = 0.86; $\chi^2 = 17.13$, $p < .001$) all but one brain (93% correct classification). When the four variables were allowed to enter (with maximum steps set at 2 because of the sample size), the combination of the reduced damage in the ventral reuniens and increased damage in the amygdalohippocampal area resulted in a canonical correlation of 0.92 ($\chi^2 = 22.90$, $p < .001$).

The function accurately classified all of the cases. When the factor score for the four variables were employed, 85% of the shared

variance of these structures was accommodated by the ketamine treatment. There was no overlap ($F(1,13) = 70.63$, $p < .001$) in the z-scores (factor scores) for the rats that had received the ketamine and the rats that had received the acepromazine. The mean and standard deviation for the factor scores for the acepromazine group was .7 and .4 while these values for the ketamine group was – 1.1 and .3.

Symmetrical analyses of variance and covariance whereby the variance for each of the four structures was first removed from each of the other structures (before the treatment effect was analyzed) indicated that the damage within the lateroposterior thalamus was contingent upon damage within the ventral nucleus reuniens. Whereas the magnitude of the significant differences between the ketamine-treated and acepromazine-treated rats for either the amygdalohippocampal transition area and the ventral nucleus reuniens did not change when the shared variance with the other structure was first removed, the statistically significant treatment differences for the amount of damage within the laterodorsal nucleus and amygdalohippocampal transition area were eliminated when either structure was first covaried.

In order to obtain the strongest and most conservative associations between the amount of neuronal loss within the specific structures and the deficits for spatial memory, nonparametric correlations (Spearman rho) were completed for the 15 rats in which seizures had been induced. The correlation coefficients are shown in Table III for structures within the left and the right side of the brain that showed the strongest ($p < .01$) effects. The average numbers of errors (mean of working and reference errors) during the 10 days of testing were most correlated with the neuronal loss within the CA2 portion of the hippocampus and amydalostriatal transition area in the right hemisphere, the dorsal portion of the medial geniculate in the left side of the brain and the central mediodorsal and centromedial nucleus of the thalamus.

The results of the analysis of covariance which removed the shared variance between the damage within the structures that most differentiated the treatment groups and the mean numbers of working and reference errors before comparison of treatment differences were clear. Removal of the shared variance between memory errors and the amount of damage within the right laterodorsal (ventrolateral part)

TABLE III The most significant ($p < .01$) Spearman ρ correlation coefficients for all rats ($n = 15$) between mean numbers of errors (working and reference) and the amount of damage within the structure for the left and right side of the brain

Structure	*Left*	*Medial*	*Right*
Presubiculum	–		.68
CA2 Hippocampus	.72		.83
Occipital Ctx 2L	.68		–
Retrosplenial granular Ctx	.65		.62
Temporal Ctx, area 2	.59		.53
Parietal Ctx, area 1	.66		.58
Ventral Pallidum	.66		–
Amydalostriatal transition	–		.77
Thalamus			
Medial geniculate (dorsal)	.78		–
Medial geniculate (medial)	–		.72
Posterior thalamic group (triangularis)	.75		–
Laterordorsal nuc. (ventrolateral part)	.70		–
Intrathalamic medullary	.65		.65
Paraventricular nuc. (posterior part)	–		.72
Central medial thalamus	–	.75	–
Paracentral nuc.	.64		–
Intermediodorsal nuc.	–	.73	–
Anterioventral (ventrolateral part)	.66		–

Blank indicates the coefficient was not $p < .01$.

thalamus, right lateral posteriomedial thalamus (rostral part), right temporal cortices, and CA2 region of the right Ammon's Horn completely eliminated the statistically significant differences in the numbers of maze errors between the acepromazine and ketamine treated groups ($Fs(1,12)$ $1.00 > p > .05$). The initial removal of the shared variance with damage within the amygdalohippocampal transition area, however, did not change the level of statistical significance of the treatment differences for maze errors.

DISCUSSION

The results of this study indicated that administration of the dosage of ketamine (100 mg/kg) employed by Fujikawa (1995, 1996) 30 min after the overt display of forelimb clonus and beginning of status epilepticus (SE) was only partially neuroprotective. There was no statistically significant difference between the ketamine-treated and

acepromazine-treated rats for the *average* damage within *all* of the structures examined within either the left or right sides of the brain. Most of the structures that displayed neuronal loss following SE were not affected significantly by the ketamine. Only about ten structures within the thalamus and area 1 of the parietal cortices showed moderate (but not total) neuroprotection by this ketamine treatment. Because Fujikawa (1995, 1996) also injected his seized rats with the muscarinic cholinergic antagonist methylatropine, diazepam and phenobarbital, the degree of neuronal protection by ketamine observed in his studies may require all of these compounds to be injected following the onset of the seizures.

The brain structures that were protected in the present study were those that might be considered mediators of emotional arousal through thalamolimbic connections such as the reuniens-hippocampal pathways. Other structures, such as the entorhinal cortices and the amygdalohippocampal interface, showed *greater* damage in the rats that had been treated with ketamine compared to acepromazine. While acepromazine-treated rats displayed the usual episodes of spontaneous seizures (overt rearing, forelimb clonus and loss of balance) during casual periods of maintenance and testing for weeks after they had "recovered" from SE, the ketamine rats never displayed these overt indicators. We suggest that the enhanced damage within the amygdalohippocampal area and entorhinal cortex of the rats that received the ketamine may have reduced the electrical lability within these regions.

Rats in which SE has been induced by muscarinic agents frequently exhibit, recurrent overt seizures. These anomalies emerge after a "quiet period" in the order of about two weeks (Cavalheiro *et al.*, 1991; Girgis, 1986) at about the time other aberrant behaviours become conspicuous (Persinger *et al.*, 1988, 1993). This silent period may be associated with recurrent electrical seizures that result in natural kindling. In fact the overt characteristics of the spontaneous seizures in these rats are indistinguishable from the Racine (1972) level 4 and 5 seizures (forelimb clonus, loss of balance) as well as the occasionally level 6 seizures (tonic–clonic convulsion) induced by recurrent electrical stimulation by implanted electrodes. That experimental lesions of regions that block the pathways involving the amygdalohippocampal and entorhinal cortex can markedly reduce

the likelihood of kindling-induced seizures has been reported (Heinemann *et al.*, 1993; McIntyre and Plant, 1989).

If the poor maze performance displayed by the acepromazine-treated rats 30 days after seizures was due to recurrent subclinical electrical seizures that interfered with consolidation of memory, then enhanced damage to the entorhinal–amygdalohippocampal region may have minimized these disruptions. On the other hand the marked neuroprotection of the nucleus reuniens, a direct modulator of the electrical activity within the CA4 and CA3 regions of the hippocampal formation, could have protected the electrically labile "ensemble" or engram that exists transiently after the acquisition of new information.

Analyses of variance and covariance, by which the shared variance between errors displayed within the maze over 10 days and the proportion of neuronal loss within a structure was first removed (before the comparison of treatment effects were discerned), would support the second explanation. Covariance for the amount of damage within the amygdalohippocampal region did not alter the significant difference in errors displayed by the groups that received either ketamine or acepromazine after the induction of the seizures. However this treatment effect was eliminated if the shared variance between the amount of damage within structures in areas known to be associated with maze acquisition of memory, specifically the right laterodorsal thalamus and right CA2 region of the hippocampus, was first removed from the analysis.

These results indicated that the normal maze performance by the ketamine rats was not due to increased damage within the amygdalohippocampal region but was associated with sparing of neurons within the specific regions of the hippocampus and thalamus that are known to be associated with proficient maze performance. One interpretation of the results of the analysis of variance and covariance between the three thalamic structures (laterodorsal thalamus, lateroposterior nucleus, and ventral nucleus reuniens) and the amygdalohippocampal region and the factor analysis is that the neuroprotective effect of neurons within the reuniens and the exacerbation of damage within the amygdalohippocampal region were not causal but coupled to a third factor that produced both effects independent of each other (Barbarosie and Avoli, 1997; Dolleman-van der Weel *et al.*, 1997).

On the other hand the enhanced damage within the amygdalohippocampal transition area and savings within the laterodorsal nucleus of thalamus was significantly correlated. These results would indicate that the relative savings of the nucleus reuniens and the laterodorsal thalamus facilitated both short-term and long-term memory for this task, and, a by product of the greater correlative damage within the amygdalohippocampal region was the probable elimination of "post-recovery" spontaneous seizures.

The effect size of the ketamine treatment upon these few neuronal structures was large. Discriminant analysis indicated that the neuroprotective effect of ketamine upon the nucleus reuniens was sufficient to correctly classify all but 1 of the 15 rats. The factor extracted from the shared variance between the three thalamic and one limbic region was sufficient to accurately identify all of the rats according to their treatments. The effect size was equivalent to a correlation coefficient of $r = 0.92$.

From a neurobehavioral perspective the fact that a group of rats which received the ketamine and exhibited marked general neuronal loss displayed numbers of errors that were not significantly different from controls within a complex spatial task requiring both learning and memory is important. The results indicate that either post-seizure ketamine treatment can mask the adverse behavioral effects of this damage or the structures protected by the ketamine were serendipitous to the task (spatial memory) chosen to discern the behavior impact of this treatment. Whether or not rats that had been seized with lithium/pilocarpine and treated with ketamine display normal scores within other paradigms and show increased vulnerability to complex magnetic fields that may directly influence the modified neuromatrix induced by these chemical treatments must still be examined.

References

Barbarosie, M. & Avoli, M. (1997) CA3-driven hippocampal-entorhinal loop controls rather than sustains *in vitro* limbic seizures. *Journal of Neuroscience*, **17**, 9308–9314.

Cavalheiro, E. A., Leite, J. P., Bortolotto, Z. A., Turski, W. A., Ikonomidou, C. & Turski, L. (1991) Long term effects of pilocarpine in rats: structural damage of the brain triggers kindling and spontaneous recurrent seizures. *Epilepsia*, **32**, 778–782.

Dolleman-van der Weel, M. J., Lopes da Silva, F. H. & Witter, M. P. (1997) Nucleus reuniens thalami modulates activity in hippocampal field CA1 through excitatory and inhibitory mechanisms. *Journal of Neuroscience*, **17**, 5640–5650.

Fujikawa, D. G. (1995) Neuroprotective effect of ketamine administered after status epilepticus onset. *Epilepsia*, **36**, 186–195.

Fujikawa, D. G. (1996) The temporal evolution of neuronal damage from pilocarpine-induced status epilepticus. *Brain Research*, **725**, 11–22.

Girgis, M. (1986) Biochemical patterns in limbic system circuitry: biochemical–electrophysiological interactions displayed by chemitrode techniques. In: Doane, B. K. and Livingston, K. E. (Eds.), pp. 55–56, *The limbic system: functional organization and clinical disorders*. New York: Raven Press.

Handforth, A. & Treiman, D. M. (1995) Functional mapping of the late stages of status epilepticus in the lithium–pilocarpine model in rat: a 14C-2-deoxyglucose study. *Neuroscience*, **64**, 1075–1089.

Harrigan, T., Peredery, O. & Persinger, M. A. (1991) Radial maze deficits and mediodorsal thalamic damage in context of multifocal, seizure-induced brain lesions. *Behavioral Neuroscience*, **105**, 482–486.

Honchar, M. P., Olney, J. W. & Sherman, W. R. (1983) Systemic cholinergic agents induce seizures and brain damage in lithium-treated rats. *Science*, **220**, 323–325.

Heinemann, U., Li Zhang, C. & Eder, C. (1993) Entorhinal cortex–hippocampal interactions in normal and epileptic temporal lobe. *Hippocampus*, **3**, 89–98.

McIntrye, D. C. & Plant, J. R. (1989) Pyriform cortex involvement in kindling. *Neuroscience and Biobehavioral Reviews*, **13**, 277–280.

Olton, D. S., Becker, J. T. & Handelmann, G. E. (1979) Hippocampus, space, and memory. *Behavioral Brain Science*, **2**, 313–365.

Paxinos, G. & Watson, C. (1986) *The rat brain in stereotaxic coordinates*. Toronto: Academic Press.

Peredery, O., Persinger, M. A., Blomme, C. & Parker, G. (1992) Absence of maternal behavior in rats with lithium/pilocarpine seizure-induced brain damage: support of MacLean's triune brain theory. *Physiology and Behavior*, **52**, 665–671.

Persinger, M. A. (1979) Brain mast cell numbers in the albino rat: sources of variability. *Behavioral Neural Biology*, **25**, 380–386.

Persinger, M. A., Bureau, Y. R. J. & Peredery, O. (1994) Dissociation between conditioned taste aversion and radial maze learning following seizure-induced multifocal brain damage: quantitative tests of serial *vs.* parallel circuit models of memory. *Physiology and Behavior*, **56**, 225–235.

Persinger, M. A., Bureau, Y. R. J., Kostakos, M., Peredery, O. & Falter, H. (1993) Behaviours of rats with insidious multifocal brain damage induced by seizures following single peripheral injections of lithium and pilocarpine. *Physiology and Behavior*, **53**, 849–866.

Persinger, M. A., Makarec, K. & Bradley, J.-C. (1988) Characteristics of limbic seizures evoked by peripheral injections of lithium and pilocarpine. *Physiology and Behavior*, **44**, 27–37.

Persinger, M. A., Peredery, O., Bureau, Y. R. J. & Cook, L. L. (1997) Emergent properties following brain injury: the claustrum as a major component of a pathway that influences nociceptive thresholds to foot shock in the rat. *Perceptual and Motor Skills*, **85**, 387–398.

Persinger, M. A., Peredery, O., Desjardins, D. & Eastman, A. (1998) Ventricular dilatation over several weeks following induction of excitotoxic (systemic lithium/pilocarpine) lesions: potential role of damage to the substantia nigra reticulata. *International Journal of Neuroscience*, **94**, 63–74.

Racine, R. J. (1972) Modification of seizure activity by electrical stimulation: II Motor seizures. *Electroencephalography and Clinical Neurophysiology*, **32**, 281–294.